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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)

0652.2040000/JMC/KBK

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on _____

Signature _____

Typed or printed name _____

Application Number	Filed
09/500,991	February 15, 2000

First Named Inventor: Frank Uhlmann

Art Unit	Examiner
1652	Fronda, Christian

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- [ ] applicant/inventor.
- [ ] assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- [X] attorney or agent of record. Registration number 38,759.
- [ ] attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

John M. Covert
Signature

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January 7, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

[X] *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:	Confirmation No.: 3282
Uhlmann *et al.*	Art Unit: 1652
Appl. No.: 09/500,991	Examiner: Fronda, Christian
Filed: February 15, 2000	Atty. Docket: 0652.2040000/JMC/KBK
For: **Compounds Modulating Sister Chromatid Separation and Method for Identifying Same**	

Arguments to Accompany the Pre-Appeal Brief Request for Review

Mail Stop AF

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby submit the following Arguments, in five (5) or less total pages, as attachment to the Pre-Appeal Brief Request for Review (Form PTO/SB/33). A Notice of Appeal is concurrently filed.

Summary of Request

The Examiner's rejection of claims 36, 37, 40, 41, 43, 44, 46-49 and 58 under 35 U.S.C. § 103(a) as being unpatentable over Brown *et al.* (Analytic Biochem. 217(1):139-147, 1994, hereinafter "Brown") in view of Nagase *et al.* (DNA Res. 3(1):17-24, 1996, hereinafter "Nagase") and Nomura *et al.* (DNA Res. 1(5):223-229, 1994, hereinafter "Nomura") is improper. Specifically, the Examiner erred by using the inventor's own disclosure, and the inventor's own work published after the effective filing date of the application (Waizenegger *et al.* (Cell. 2000 Oct 27; 103(3):399-410), Sumara *et al.* (J Cell Biol. 2000 Nov 13; 151(4):749-62), and Hauf *et al.* (Science. 2001 Aug 17; 293(5533):1320-1323)), to provide the reason that a person of skill in the art would be motivated to combine the cited references. Thus, Applicants respectfully request that the obviousness rejections be withdrawn and the claims allowed.

Arguments

The Examiner maintained the improper rejection over the combination of Brown, Nagase and Nomura in the Office Action of September 7, 2007. Brown discloses a high-throughput fluorometric process for measuring protease activity comprising contacting a peptide with a

protease in the presence of an inhibitor test compound. The peptide is a fluorogenic peptide labeled at one end with a UV/blue fluorophore and at the other end with a quencher. As the Examiner notes, Brown does not teach incubating a separin and a separin substrate in the presence of a test compound. Nagase teaches the cDNA KIAA0165, disclosed in the Applicants' specification to encode the human separase. Nomura teaches the cDNA KIAA0078, disclosed in the Applicants' specification to encode the human SCC1. Neither Nagase nor Nomura indicate a function for the cDNAs described therein. The Examiner concludes,

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the process of Brown et al. such that the human separin taught by Nagase et al. and the human SCC1 taught by Nomura et al. is used in the process taught by Brown et al., where the human SCC1 is labeled at one end with a UV/blue fluorophore and at the other end a quencher.

(*Id.* at p. 3.)

In order to establish a *prima facie* case of obviousness, it must be shown that the claimed invention as a whole would have been obvious from the disclosures and teachings of the prior art. A *prima facie* case of obviousness has not been established. In order to practice the method of Brown, the skilled artisan must have knowledge of a protease and its substrate. Brown states,

> Although used here specifically for the enzyme which cleaves at the amino terminus (N-terminus) of β-amyloid peptide (BAP), this type of radiolabeled substrate is readily applied to the analysis and detection of other endoprotease activities. This method relies on a peptide substrate which contains: (a) the amino acids flanking the enzymatic cleavage site . . . .

(*Id.* at p. 139.)

The Examiner relies on the disclosures of Nomura and Nagase as allegedly teaching human separase, a protease, and the human separase substrate, SCC1. Applicants respectfully disagree with this assertion. Nomura and Nagase teach nothing more than the predicted coding sequences of 80 uncharacterized human genes. There is nothing in Nagase to suggest that the predicted KIAA0165 protein is a protease. Nagase does not disclose any structural motifs, perform any experimentation that would suggest a function, or even hypothesize a role for the predicted KIAA1065 protein. Likewise, there is nothing in Nomura to suggest that the predicted KIAA0078 protein is a protease substrate. In fact, Nagase and Nomura do not even present evidence that KIAA0165 or KIAA0078 are translated into protein. Thus, to a person of ordinary

skill in the art, KIAA0165 and KIAA0078 simply represent two of eighty uncharacterized human cDNAs that may or may not be translated into a protein of unknown function.

In response to the Applicant's arguments of June 6, 2007, the Examiner stated,

> [I]t must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and *does not include knowledge gleaned only from the applicant's disclosure*, such a reconstruction is proper.

(*Id.* at p. 3, emphasis added)

Applicants submit that the Examiner has in fact relied on knowledge gleaned only from the Applicants' own work to formulate an obviousness rejection. Before Applicants' disclosure of the present invention, it was not known that separase was a protease, and it was not known that SCC1 was a separase substrate. Without that knowledge, no reason existed at the time of the invention to combine the teachings of Brown with the teachings of Nagase and Nomura. The Examiner has improperly relied upon the teachings of Waizenegger *et al.* and Sumara *et al.* for evidence that KIAA0165 is the human separase and a protease and that KIAA0078 is the human SCC1 and the substrate of separase. These publications were published by the Applicants' research group after the filing date of the present application, and thus are not available as prior art under any section of 35 U.S.C. 102. Applicants' discoveries, as later reported in Waizenegger *et al.* and Sumara *et al.*, form the basis of the present invention. The use of the Applicants own disclosures to form the basis of an obviousness rejection constitutes impermissible hindsight. It is well established that the reason to combine references, as evidence of obviousness, must come from the prior art. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." (See MPEP 2143; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, Fed. Cir. 1991.) "[I]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. . . . This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.' " (*In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780, Fed. Cir. 1992.) Without Applicants' disclosure, what would lead a skilled artisan to select, out of the myriad of known cDNA sequences and the amino acid sequences encoded thereby, KIAA0165 and KIAA0078?

The rejection is not supported by any evidence or explanation as to why a person of ordinary skill in the art, at the time of the invention, would have reason to believe that the KIAA0165 protein is a protease and that the KIAA0078 protein is the substrate of the KIAA0165 protein. Without such knowledge, one of ordinary skill in the art would have lacked any reason to conduct an assay employing KIAA0165 as a protease and KIAA0078, or a fragment thereof, as a substrate. To combine references without evidentiary support, at least some suggestion or reason found within the prior art, constitutes impermissible hindsight. "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art." *KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1740-41, 82 USPQ2d 1385, 1396 (2007).* Furthermore, a person of ordinary skill in the art would not have been motivated to combine these references with a reasonable expectation of success.

As discussed in MPEP § 2143.01, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The Examiner has put forth no reason or motivation to combine Brown with Nagase and Nomura that does not improperly rely on the Applicants' own disclosure. In the September 2, 2007, final Office Action, the Examiner argued the following as a motivation to combine references:

> One of ordinary skill in the art at the time the invention was made would have been motivated to do this for the purposes of having an fast and simple process for identifying human separin inhibitors, which can be used as anti-cancer agents that inhibit sister chromatid separation in cancer cells.

(*Id.* at page 3)

This reasoning relies upon the knowledge that separase is a protease and that SCC1 is its substrate, knowledge revealed for the first time in Applicants' disclosure.

The Examiner further implies that the properties of separase and SCC1 were inherent in the prior art. "Nagase et al. teach the human separin encoded by cDNA KIAA0165 which inherently has protease activity. . . . Nomura et al. teach the human SCC1 encoded by cDNA KIAA0078 which inherently is a protease substrate for human separin." (*See* Office Action at p.

4.) However, an obviousness argument cannot be based on inherent properties in the prior art when there is no motivation to combine references. "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." See *In re Spormann*, 53 CCPA 1375, 363 F.2d 444, 150 USPQ 449 (1966).

Conclusion

The Examiner has not presented a proper *prima facie* case of obviousness based on the combination of Brown, Nagase and Nomura. The Examiner has legally erred by using the Applicants' own disclosure as a template to pick and choose among isolated disclosures in the prior art, which constitutes impermissible hindsight. No logical motivation to combine these references, constructed from evidence found in the prior art, has been presented.

Summary

For the reasons set forth above, the Examiner's rejection of the pending claims under 35 U.S.C. § 103(a) is legally flawed, and the Examiner has not established a proper *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the obviousness rejection be withdrawn and the claims allowed.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

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